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Preliminary Observations on the Effect of Adrenocorticotropic Hormone (ACTH) in Allergic Diseases: Because the experimental studies of Rich and Gregory suggest a relationship between the hypersensitive state and the rheumatic diseases, the possible usefulness of ACTH in the control of the hypersensitivity state was first explored in a patient with severe exfoliative dermatitis caused by iodine. The unique rapidity of recovery in this critically ill patient stimulated the trial of ACTH in other allergic states. In the second patient extensive giant urticaria, joint pains, and fever associated with a serum-disease-type sensitivity to penicillin were abolished within 24 hours after ACTH was begun.

The prompt control of the chronic asthmatic state and the striking alterations in the tissues of the upper respiratory tract in 5 asthmatic patients form the basis of this preliminary report. In 2 patients the asthma was thought to be caused by combined external and intrinsic factors. In the other 3 it was of the intrinsic type. The age of the patients ranged from 26 to 63 years, and the duration of the asthma from 5 to 23 years. The sputum in all contained many eosinophils. In several of the patients no more than partial and very temporary relief was obtained by the administration of adrenalin, aminophyllin, and ether by rectum. The initial daily dose of ACTH varied between 30 and 100 mg. given intramuscularly, divided in equal portions at 6-hour intervals. Unequivocal benefit was noted in from 4 to 48 hours. Complete freedom from all asthmatic symptoms occurred within from 1 to 8 days. In 4 of the patients there was total disappearance of sputum and abnormal physical signs in the chest. In the fifth patient, who was 6 months pregnant, rhonchi persisted although she was free of asthmatic symptoms. Treatment was maintained for from 11 to 21 days. The daily dose was gradually reduced after clinical recovery; the total amount administered ranging from 360 to 775 mg. One patient has remained asymptomatic for one month after discontinuing therapy.

Detailed examinations of the upper respiratory tract, including nasopharyngoscopy, were made on 4 of the patients. Three patients had a pale, edematous polypoid nasal mucous membrane which was bathed with a thick mucopurulent discharge. During therapy the membrane became bluish pink in color, was covered with clear mucus, and the edematous, polypoid appearance was no longer present. The breathing space was greatly enlarged. The lymphoid tissue in the nasopharynx, which was covered with a thick discharge, was pale and edematous. During treatment the edema subsided, an orange pink color developed, the crypts became more prominent, and it was easily outlined from the surrounding mucous membrane. There was no gross change in the volume of the lymphoid tissue present. In 2 patients there was complete obstruction of the nose by polyps. These began to shrink on the third day of treatment and by the end of therapy .

had completely vanished in one patient and almost completely in the other. The 3 patients with mucous membrane abnormalities had antral clouding on roentgenological examination which cleared during the administration of ACTH. Several small polyps had reappeared in one patient on the twenty-third day after cessation of therapy.

The intradermal reactions to inhalant and bacterial antigens were followed in 3 patients. Two showed marked skin sensitivity to pollens and other extrinsic antigens. In one the sensitivity was greatly diminished during treatment but returned to its original level 3 weeks after cessation of ACTH. In the other patient no alteration was observed. In both patients serum reagin titration revealed no change. The intradermal reaction to bacterial antigens decreased significantly in 2 patients and did not change in another. In one the sensitivity has returned to the pretreatment level 3 weeks after discontinuance of ACTH.

These clinical studies suggest that ACTH may have an important action in blocking various hypersensitivity reactions. Further observations are necessary to establish its efficacy in allergic states, and the effects of ACTH in other types of hypersensitivity are under study. (Bull. Johns Hopkins Hosp., Nov. '49, J. E. Bordley et al.)

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Electrocorticography: The recording of the electrical changes of the brain by electrodes placed directly upon the cerebral cortex has been termed electrocorticography. Although such technics have been used in animals since the beginning of electroencephalography, in man the procedure has only recently been carried out extensively. Its use is much more limited than electroencephalography, because, when the brain is exposed, the lesion is usually apparent. Yet electrocorticography has a definite place in neurological surgery, being of great value in anatomical and physiological studies of the cortex, in the localization of subcortical tumors, and in the determination of epileptogenic foci.

In early work the electrodes were merely laid on the cortex and not mounted on the skull. Surprisingly good records were obtained by this technic but the number of electrodes used was usually limited, only 2 being present on the cortex at once. For multiple recording some type of electrode holder, capable of being firmly clamped to the skull, is necessary. Several such types of assembly have been employed, perhaps the earliest being that used by Jasper. There are a number of models available at this time; all have similar principles but vary in design. The one used in the clinic at the Johns Hopkins Hospital was devised by one of the authors and consists of a lucite plate in which from 10 to 16 fine tubular electrodes are inserted, each upon a universal joint. The plate is attached to the skull by a clamp. Contact with the cortex is made by small silver balls mounted on very

light springs at the ends of wires floating in the tubular probes so that the pressure upon the cortex is always light. In some electrodes the cortical contact consists of a wick which is kept moist. The electrodes should be freely movable so that they may be placed at any point over a wide area of the cortex.

Although a completely shielded room is desirable, electrocorticography may be carried out in the ordinary operating theatre with a good electroencephalograph, provided a few precautions are observed. The patient and operating table should be grounded to the electroencephalograph. Electrosurgical units, electric motors and sometimes the electric lights of the room must be disconnected at the wall plug. With these special arrangements usually a good record from the cortex may be obtained free of artifact. If spikes interfere in all channels, an electric motor from 30 to 50 feet away in an adjoining room may be at fault.

Electrocorticography is particularly valuable in the localization of epileptogenic foci. cortical exploration should be carried out under local anesthesia. The epileptogenic focus may be determined by (1) focal spontaneous spiking, (2) induction of a convulsive aura by the electrical stimulation of the cortex, (3) production of a long lasting after-discharge, and (4) by the initiation of spiking by local or systemic administration of metrazol. (Bull. Johns Hopkins Hosp., Nov. '49, C. Marshall and A. E. Walker)

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An Evaluation of Radical Surgery for Carcinoma of the Pancreas and Ampullary Region: Radical surgery has been made possible by a better understanding of supportive treatment, blood transfusion, maintenance of fluid, protein and electrolyte balance, improved methods of anesthesia, and proper use of chemotherapeutic agents.

In the early thirties, successful removal of islet cell tumors demonstrated that the pancreas was not an untouchable organ. In March of 1940, when vitamin K had become available for control of the bleeding tendency, the author and co-workers carried out the first one-stage resection of the head of the pancreas with all of the duodenum, the antrum of the stomach, the lower end of the common duct and the retroduodenal lymph-node-bearing area in a woman with a carcinoma of islet tissue. This patient is still alive and active.

Since 1940, many modifications of the one and 2-stage radical procedures have been successfully carried out, some 220 of them in 5 of the clinics of this country. Furthermore, since Priestley's first total pancreatectomy for hyperinsulinism in 1944 (this patient is alive and well, requiring only from 20 to 30 units of insulin per day) some 20 others have been reported.

Cancer of the papilla of Vater and the ampullary area is usually a fungating adenocarcinoma, growing into the lumen of the duodenum with a slower invasion of the lymphatics. Carcinomas of the pancreas are more often of the invasive, infiltrating, undifferentiated type, spreading rapidly into the lymph nodes and metastasizing to the liver and pertioneum. Ampullary growths obstruct the bile and pancreatic ducts more quickly and completely than those in the pancreas, and give the important warning signal of jaundice earlier. Courvoisier's syndrome of painless jaundice with an enlarged gall bladder is most frequently seen in the patients with ampullary tumors; however, not all of these patients are pain-free, yet the pain is not as severe, constant, or radiating to the back as it is in carcinomas of the body or tail of the pancreas. The occurrence of jaundice as a warning signal in carcinoma of the pancreas depends upon the proximity of the growth to the common duct; it is usually absent in carcinoma of the body and tail. In carcinoma of the pancreas, pain, as mentioned, is usually more severe and constant, worse on lying down and frequently of a boring character, radiating into the back. The more distant from the ampulla, the later the diagnosis as a rule, and the worse the prognosis.

Aside from the history and physical examination, which in many patients establishes the early diagnosis, certain laboratory procedures are helpful and must be emphasized. The most important is the study of the duodenal contents. In aspirating the fasting duodenal contents by the double tube Lagerlof technic, the important findings are the amount of bile and presence or absence in it of cholesterol crystals and bile pigment particles, the amount or absence of pancreatic juice, the presence of red blood cells, and the presence of tumor cells. Marked diminution or absence of bile and pancreatic juice, with the presence of red blood cells or tumor cells, indicates a carcinoma of the papilla. Normal amount of pancreatic juice with marked diminution or absence of bile plus red blood cells points to a carcinoma of the common duct. Normal bile but diminished or absent pancreatic juice plus red blood cells implies a carcinoma of the pancreas. Cholesterol crystals or bile pigment particles indicate the presence of gall stones. The finding of tumor cells in the centrifuged specimens establishes the diagnosis of neoplastic disease. Jaundice with an elevated serum phosphatase means obstruction of the common duct. Absence of jaundice does not rule out a growth in the pancreas. Careful barium roentgen-ray studies of the duodenum may show a filling defect caused by a fungating growth of the ampulla, or a distortion or increase in the C-curve of the duodenum, resulting from a tumor in the head of the pancreas.

The only hope for obtaining good results from radical surgery in these cancers lies in the early diagnosis of localized lesions. In the majority of cases, the general practitioner and the internist are first consulted, and thus become responsible for prompt and early diagnosis, or a fatal delay by studying the patient until the diagnosis is obvious and the lesion inoperable.

The average life expectancy in patients with carcinoma of the pancreas treated expectantly is about 6 months. A palliative bile shunting operation, preferably a cholecystojejunostomy, relieves the patient of intolerable pruritus and temporarily improves digestion, and should be done if the growth is found to be inoperable.

During the first 10 years of this radical surgery, the operative mortality rate was in the 30-percent level; but with the improvements in pre- and postoperative therapy and in the operative technic, the mortality rate has been markedly reduced. Cattell has the remarkable record of a 13.6 percent mortality rate in 59 patients. He has carried out pancreatoduodenectomy in 22 patients with ampullary growths, with only one death. Parsons and Lockwood have not lost a patient in their last 13 radical procedures. Waugh of the Mayo Clinic has lost only one patient in the last 15 pancreatoduodenectomies.

The radical surgery for ampullary carcinoma gives better results than for carcinoma of the pancreas itself. From the clinics mentioned, 8 patients lived 5 years or more, after removal of ampullary growths, 2 of them over 7 years. Of the collected cases of carcinoma of the pancreas, 3 patients have survived 5 years or more, 2 of them operated upon by Brunschwig. One of these, in whom the first one-stage radical resection for carcinoma of islet cells was performed, has lived over 9 years, but may have liver metastases at present. This is not a functioning islet cell tumor, however. In Cattell's series of 59 patients operated upon for carcinoma, 30 percent have lived 3 years or more.

The fact that it has been demonstrated that cancer cells can be readily found in pancreatic duct fluid in cases of pancreatic carcinoma, and that trypsin favors the transplantation of cancer cells in experimental animals would explain the high incidence of recurrence associated with resection of the pancreas, and may be a definite indication for a total pancreatectomy in patients with carcinoma of the pancreas. (Ann. Int. Med., Oct. '49, A. O. Whipple)

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Evaluation of a New Agent (Methyl-Iso-Octenylamine) in the Treatment for Vasolilating Headaches: Several investigators recently have reported favorable results with the use of octin (methyl-iso-octenylamine) in the treatment for migraine and related vasodilating headaches.

Only those patients with a definite diagnosis of migraine headache, histaminic cephalalgia, or tension headache were selected for this study, and only patients with acute attacks were treated. Special care was taken to ascertain that none of the patients had taken any other form of medication prior to the administration of octin. Octin can be administered either intramuscularly or orally, but not intravenously. Octin hydrochloride, in a concentration of 100 mg. per cubic centimeter of solution, was administered intramuscularly to one group of patients in from 0.5 to 1.0 cc. doses

as early as possible in the attack of headache. If no relief from pain occurred, the dose was repeated in 30 minutes. Later in the study the initial dose of 0.5 was changed to 1.0 cc. because no serious untoward reactions were encountered. The oral preparation used in this study was octin mucate. One tablet containing 2 grains (0.13 Gm.) of octin mucate was administered every 30 minutes until relief was obtained. No more than 4 tablets were employed in the treatment for any one attack.

The amount of relief obtained and any recurrences of pain were recorded. No headache which required longer than 2 hours to be relieved with the use of octin was included in the series. Each patient was carefully observed for the appearance of the known side effects of the drug, namely, transient hypertension, nausea, vomiting, palpitation, weakness, nervousness, sense of fainting, and paresthesias of the face and arm.

For the intramuscular series, of 59 headaches partial or complete relief was obtained in 48, and no relief in 11. Ten headaches recurred. For 7 of the headaches, repeated doses of octin had to be used. No benefit was obtained in two of these headaches even after repeated trials of medication. No toxic or side reactions of the drug were observed except in 6 normotensive patients in whom transient hypertension developed during treatment. The average increase in blood pressure in the 6 patients was 35 mm. of mercury systolic and 25 mm. diastolic. The authors do believe, however, that it is not a wise policy to administer octin to patients with pre-existing hypertension.

In 26 headaches, for which octin was administered orally, complete or partial relief was obtained in 15 and there was no relief in 11. Headache recurred in one patient. No toxic reactions were observed. Transient hypertension did not occur in any of the patients who received octin by mouth.

Octin relieves the pain of vasodilating headaches by acting as a vasoconstricting agent. The basic mechanism for this vasoconstriction, however, is not clearly understood at present but 2 theories have been advanced to explain its action; one is that it produces stimulation of the sympathetic nervous system, and the other is that it acts directly on the muscles of the blood vessels to cause constriction. Based upon their own work and that of others, the authors believe that about 50 percent of the patients may expect complete relief from headaches when octin is administered intramuscularly. Although octin administered orally seems to be of some help, the authors have not been impressed with its effectiveness in aborting acute attacks of headaches. They have gained the impression that best results with this drug may be expected in the treatment for the typical migraine attack and that poorer and more varying results may be anticipated in the treatment for the headache caused by nervous tension.

Octin does not appear to be the drug of choice in the treatment for all patients with migraine and related headaches. Octin, unlike the ergotamine preparations, cannot be given intravenously. This is a disadvantage when prompt action is desired. Furthermore, the authors have gained the impression from reports by patients who have had experience with both ergotamine preparations and octin that the former act more quickly and effectively. Orally administered octin does not seem to give as consistent relief as E. C. 110 (1 part ergotamine tartrate plus 100 parts of caffeine), which is now on the market under the trade name of cafergone (Sandoz Chemical Co.). However, octin administered intramuscularly is suitable for use in a carefully selected group of patients, those normotensive patients in whom it really produces effective relief and in those individuals who do not obtain symptomatic relief from the use of the more conventional drugs such as ergotamine tartrate (gynergen) and dihydroergotamine (DHE 45). It is of particular value in those patients who may have abused the use of the ergotamine preparations and in those for whom the use of ergotamine may be considered as contraindicated. (Pro. Staff Meet. Mayo Clinic, 9 Nov. '49 G. A. Peters and W. W. Zeller).

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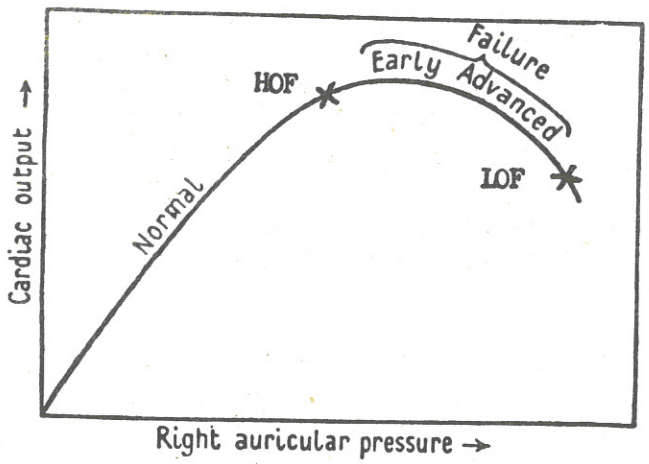
New Light on the Pharmacodynamics of Heart Failure: Since Withering established the empirical fact that the powdered leaves of foxglove were a valuable remedy for the dropsy, many of the pharmacological actions of digitalis have been elucidated. Those that have gained general acceptance are summarized by Willius in 3 main compartments: (1) digitalis depresses the function of the sino-auricular and the auriculo-ventricular nodes, and a tendency to slowing of the cardiac rate results; (2) it depresses conduction throughout the cardiac muscle, particularly through the auriculo-ventricular bundle, and increases the refractory period in both the auricles and ventricles; (3) it increases the amplitude of cardiac contraction and tends to restore tonus, apparently through a direct action on the heart muscle. The therapeutic applications of digitalis are each based on one or more of these accepted actions. Thus, in auricular fibrillation it is effective by depressing AV conduction, with consequent slowing of the ventricles. In sinus tachycardia, on the other hand, if it acts at all to slow the heart, it functions by increasing vagal tone and depressing the SA node. In congestive heart failure many actions have been ascribed and disputed. Mackenzie and Lewis both considered that slowing the heart's rate was the important action. It has also been widely thought to exert its main effect by a direct action on the myocardium, either by increasing the force of systolic contraction or by increasing diastolic tonus, or by both. Recent experimental work has cast doubt on all these concepts. Evidence is fast accumulating that its chief action is exerted elsewhere than on the heart itself.

As long ago as 1926 Harrison and Leonard showed that digitalis lowered the output of the heart in normal dogs. Dock and Tainter in 1930 demonstrated

that the venous pressure was also lowered in normal dogs by digitalis. They showed that this venous depressor action was the result of constriction of the hepatic veins, with trapping of blood in the liver and consequent diminution of the venous return. They suggested that a similar mechanism might be at work in man. Rytand in 1933 demonstrated that digitalis lowered venous pressure in normal man, and Wood in 1940 showed that the drug reduced venous pressure in patients with heart failure, independently of any change in heart rate. He also adduced evidence against the hepatic vein throttle mechanism suggested by Dock and Tainter.

Using cardiac catheterization, McMichael and his colleagues at the Postgraduate School in London made 25 series of observations on a group of 24 patients; 3 of these had normal hearts and the remainder suffered from some form and degree of heart failure. The diseased group included patients with hypertensive, valvular, and coronary disease, and others with anemia, cor pulmonale, and thyrotoxicosis. The one constantly observed effect of 1.5 mg. digoxin administered through the catheter was a fall of right auricular pressure. This occurred in each and every patient, in the normals and in those with cardiac failure alike. Cardiac output, on the other hand, behaved variously; it rose in 15, fell in 7, and in 3 there was no significant alteration. Scrutiny of these results showed that there was a nice correlation between the initial level of output, and its response to digoxin. Thus, those patients whose output had been normal or high before digoxin was administered, showed a fall in output after digitalization; this group was composed of the normal patients and those with cor pulmonale and anemia. On the other hand, those who had a low initial output responded to digoxin with a rise in output; this larger group contained the hypertensive, valvular, coronary, and thyrotoxic failures. Twelve further cases with a low initial output have subsequently been studied and reported upon. In all of these also, the right auricular pressure fell while the output rose significantly after digoxin. Based upon the results obtained, McMichael and co-workers introduced the concept of high output and low output failure. They propose that high output failure is caused by conditions which demand an increase in the output of the heart, such as anemia, emphysema, beriberi, and arteriovenous aneurysms. In this form of failure the high venous pressure is a compensatory mechanism, called into play to maintain the required high output. Whereas in the more common low output failure caused by hypertensive, valvular, or coronary disease, the high venous pressure is the result of back-pressure behind the failing ventricles.

To explain the mechanism of these 2 types of heart failure McMichael appeals to Starling's curve as shown on the next page. The heart in advanced congestive failure with a diminished output, is situated on the overloaded part of the curve; that is, at a point where the heart can no longer respond to increased venous filling by increasing its output. This may be represented by the hypothetical point LOF. The heart in high output failure, in contrast, is on the upstroke of the curve near its summit at the hypothetical point HOF.



Such a heart is still responding gallantly to the demand for high output. Now any measure which reduces venous pressure will tend to draw the heart's status back along the curve from right to left; in other words, if the heart begins af LOF and travels along the curve to the left, its output will be increased; whereas, if its starting point is HOF, the output will be diminished. And this is exactly what was found to occur with intravenous digoxin. From this McMichael suggests, logically enough, that the primary action of digitalis is to reduce venous pressure. How it acts to produce a fall in venous pressure is a matter for speculation; McMichael proposes tentatively, as the most plausible explanation, a relaxation of venomotor tone.

It could be argued that in low output failure, the fall in right auricular pressure which follows digitalization is the result and not the cause of the improved output, the output rising as a result of the stimulating action of digitalis on the ventricular muscle. The authors, therefore, investigated the effect of congesting cuffs to the thighs and venesection, both of which measures must operate primarily by reducing venous filling pressure. They found that in 4 patients subjected to congesting cuffs and in 10 subjected to venesection, the same augmentation of cardiac output occurred as was observed to accompany a similar reduction of right auricular pressure by digitalis. This finding shhws that simple reduction of venous pressure is enough to increase output, and therefore makes it at least unnecessary to hypothesize that the reduction in venous pressure is the result of increased output. Against the belief that digitalis acts as a stimulant of heart muscle, McMichael quotes the work of Katz and his associates who showed that digitalis had no effect on the contractility of isolated dog myocardium.

In this connection it is interesting to notice that many pharmacological experiments on the effects of glycosides on cardiac output have been made with strophanthin. Results obtained with this drug have sometimes been assumed to hold true for digitalis. It is therefore intriguing to find that McMichael claims, as a result of his clinical experiments, a decided difference in the effects of the 2 glycosides, digoxin and g-strophanthin, on venous pressure and cardiac output. The difference is illustrated in emphysema hearts. In these cases (high output failure) digoxin reduced the right auricular pressure and with it, in most cases, the cardiac output was lowered; whereas strophanthin often increased the output without having any appreciable influence on the right auricular pressure. He concludes that although the primary and principal

action of digoxin is to reduce venous pressure, that of strophanthin is to stimulate the myocardium. This may prove to be a point of clinical value, for although digitalis may be ineffective in cor pulmonale, and even actually harmful, strophanthin may be of definite benefit.

There are other interesting facets to McMichael's work. He has confirmed the point made by Wood that slowing of the heart by digitalis is an insignificant factor in the control of congestive failure. Wood showed that the venous pressure continued to fall in response to digitalis, even if the heart rate increased as a result of some coincident stimulus (a full bladder, atropine). McMichael has gone further and demonstrated that in failure, with either sinus rhythm or auricular fibrillation, the venous pressure falls and the cardiac output increases after digitalis, even if the heart rate increases significantly. In one notable instance of hypertensive failure, in which an urge to urinate accelerated the heart rate from 105 to 134 after the digoxin had been administered, the right auricular pressure meanwhile fell from 8 cm. to 0 cm. saline, although the output climbed from 3.05 to 5.3 liters per minute. Again he has shown that, whereas venesection and digitalis each produce similar effects on venous pressure and cardiac output, the arterial blood pressure falls with venesection but frequently rises after digoxin. Thus, although output is increased to a similar degree after both procedures, it is evident that the heart is performing more work after digitalis than after venesection. With strophanthin the pressor effect was even more pronounced, and the calculated work performed by the heart, even greater.

Applying their new technic to the investigation of theophylline-ethylenediamine (aminophylline), McMichael and his co-workers obtained further interesting results. They found that, when 0.48 Gm. aminophylline was administered intravenously to patients with hypertensive failure, the venous pressure and the cardiac output responded in the same way as to digoxin, that is, the venous pressure fell although the cardiac output rose. These effects occurred within 5 minutes in contrast with the digoxin effects which required an average of 20 minutes for their development; the cardiac output increase was also much greater than after digitalis. These aminophylline effects, however, were short-lived by comparison. Aminophylline, therefore, may be of the greatest value in instances in which a decrease in right auricular pressure is urgently needed; and, used in close succession with digitalis, a desirable summation of effects may be obtained.

In many of his experiments the small number of patients involved may well be said to render McMichael's work inconclusive. Certainly it is desirable that it be confirmed by other workers, and that much comparative work on a larger series of patients be done. The pioneer work that he has accomplished, however, is ingenious and challenging, and its significance cannot be doubted. For the moment caution must be exercised in applying his findings too closely to everyday practice for it is possible that the action of a full

digitalizing dose of digoxin delivered abruptly into the right auricle may differ importantly from the effect of a quietly cumulative assimilation of digitalis via the portal system. (Ann. Int. Med., Sept. '49, Editorial, H.J.L. M.)

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Elevation of Serum Acid Phosphatase Following Prostatic Massage: Normal serum acid phosphatase levels vary from 0.0 to 0.7, recorded in Bodansky units. High values indicate metastatic prostatic carcinoma. Fluctuations in the serum acid phosphatase levels of individual patients under altered circumstances occur and even reach high enough levels to permit an inaccurate diagnosis of metastatic carcinoma. Because of such an incident in the case of a 73 year old male patient, the authors undertook a study of the problem. In this 73 year old patient, a prostatic massage to obtain secretion for the Papanicolaou stain had preceded the drawing of blood for the phosphatase tests. The tentative explanation of the discrepancy in the acid serum phosphatase levels after errors in the laboratory procedures were ruled out was that prostatic secretion may have been massaged into the blood stream and thus produced a temporary elevation of the acid serum phosphatase. The relatively high phosphatase level 2 days later was presumably due to the patient's impaired renal function, and consequently slow excretion of the phosphatase. The authors were unable to obtain a biopsy from the prostate gland because the patient also suffered from advanced pulmonary fibrosis with cardiac decompensation. He was eventually discharged with an indwelling catheter.

Serum acid phosphatase determinations were made on 20 out-patients immediately before and at definite intervals after prostatic massage. Within one hour after prostatic massage the serum acid phosphatase was elevated above the original level in 17 patients, unchanged in 2 patients, and lower in one patient. In 8 patients the serum acid phosphatase had risen to a level above 0.7 Bodansky units, the highest level still regarded as normal. In 4 of these patients the acid phosphatase reached definite carcinoma levels (above 1.0 Bodansky units). In one patient, the relatively high figure of 0.7 Bodansky units was obtained as late as 5 hours after prostatic massage. After a 24-hour interval, the serum acid phosphatase was lower than before massage in 12 patients, not significantly changed in 6, and somewhat higher in 2 patients. After 48 hours the acid phosphatase levels were similar to the 24-hour figures. An attempt was made to correlate the character of the prostate gland with the elevation of the serum acid phosphatase after massage. In general, massage of larger prostate glands containing larger amounts of secretion seemed to produce greater acid phosphatase elevations than massage of smaller and firmer glands. In individuals with normally functioning kidneys, the acid phosphatase level is highest within one hour after the massage and may still be relatively high 5 hours after

the massage. If the kidney function is impaired, elevation of the acid phosphatase level may be prolonged.

It is concluded that serum acid phosphatase determinations should not be performed soon after a prostatic massage and that reliable and accurate values will be obtained 24 hours after massage, if the patient's kidney function is not impaired. (J. Urol., Oct. '49, E. Hock and R. N. Tessier)

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Neutralization of Three Immunological Types of Poliomyelitis Virus by Human Gamma Globulin: Recent studies of antigenic groups of poliomyelitis virus have shown the existence of at least 3 distinct types. Two of these, the Lansing and the Brunhilde, are widespread in their distribution, but the third is represented thus far by only one strain (Leon) isolated in Los Angeles, California in 1937. In an attempt to determine whether this Leon strain is perhaps unusual in its occurrence, or is sufficiently widespread to be considered of importance in the epidemiology of this disease, neutralization tests with human gamma globulin were carried out.

Pools of the viruses used are designated as Brunhilde III, Lansing VIII, and Leon I. These virus pools are of high titer, and consist of 10 or more cords of rhesus monkeys killed on the first day of paralysis. Only lumbar and cervical enlargements were used. Aqueous suspensions were prepared with a Waring blender, and aliquots sealed in glass ampules and stored on dry ice.

The globulin solution used was a sample prepared by E. R. Squibb and Sons, and supplied by the American National Red Cross who distribute it for use in the prophylaxis of measles. The human plasma pool used in the preparation of the globulin pool from which this sample was derived totalled 3,000 liters and consisted of surplus plasma returned to the American Red Cross by the Armed Forces after the war. The plasma is therefore representative of from 20,000 to 50,000 individuals who contributed blood to the Cross during the war. For the most part these individuals lived on the East Coast and in the Great Lakes Area; only a small fraction of the plasma was from blood collected in the Far West. The plasma was originally dried and subsequently reconstituted. The primary fractionation was made following method 6 of Cohn, et al.; the subfractionation was made according to method 9 of Oncley, et al. The preparation of the globulin fraction from plasma does not appear to result in deterioration of the antibody.

The results of the tests performed indicate that the neutralizing capacity of gamma globulin in this sample is very high for each of the 3 antigenic types of poliomyelitis virus. The results from the 2 sets of tests, made with separate virus aliquots, show agreement and indicate that the concentrated gamma globulin can neutralize about 30,000 PD50 of the Lansing and Leon viruses, assuming that virus and globulin dilutions are comparable. Storage of the globu-

lin solution at 4° C for almost 3 months does not appear to have impaired the neutralizing potency.

The most interesting result of these tests is that pooled adult gamma globulin may contain as much antibody against Leon virus, as against the representatives of the other 2 types, which are known to be widespread in distribution. Because relatively few strains have thus far been differentiated with respect to type, it is possible that more representatives of the Leon type will be isolated in the future. In view of the fact that only a small fraction of the plasma pool was obtained from individuals in the Far West, it seems doubtful that the Leon antibody was derived only from this source. Because the titer of Leon antibody was equal to that of the Lansing and superior to the Brunhilde virus, there seems every reason to suppose that the Leon virus type is, or was, or importance in the epidemiology of poliomyelitis. It is of further interest that the antibody against Brunhilde virus, the representative of the type currently found to be most prevalent, seemed to be present in somewhat less concentration than the antibody against the other 2 types. It is realized, however, that this preliminary study should be extended to determine in greater detail not only the geographical distribution of type-specific antibodies in human sera, but also the distribution in time and in various age groups. It is also possible to speculate that viruses of the Brunhilde type, although more prevalent than those of other types, may be inferior as antigens.

Antibody against the Lansing type of poliomyelitis virus has previously been demonstrated in human gamma globulin. The fact that antibodies against all 3 known antigenic types of poliomyelitis virus exist in high concentration in gamma globulin adds further emphasis to the report of Bahlke and Perkins, who found that relatively large amounts of this material were ineffective in the treatment for preparalytic poliomyelitis. Although elaborate controls were employed in their study, and although it is now clear that high polyvalent antibody levels are present in gamma globulin, their conclusion that serum therapy, in any form, is ineffective in poliomyelitis still seems to require some qualification. First, the type of the virus, or viruses, responsible for the cases in patients they attempted to treat was not identified, so that a remote possibility exists that specific antibody was not present in the gamma globulin used. Moreover, unconcentrated hyperimmune monkey serum contains levels of antibody approximately the same as those in human gamma globulin. Preparation of gamma globulin from hyperimmune serum could therefore be expected to produce antibody levels about 20 times greater than those found in human gamma globulin. (Pro. Soc. Exper. Biol. and Med., Oct. '49, David Bodian)

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Cultivation of Poliomyelitis Virus: Recently, the propagation in vitro of the Lansing strain of poliomyelitis virus in human embryonic tissues was reported and evidence presented that this virus is capable of multiplying in cells other than those of nervous tissue origin. These experiments have been

continued and this agent now has been carried for a total period of 224 days through 13 serial cultures in which the tissue consisted of mixed human embryonic skin and muscle. This strain also has been maintained for 173 days in 2 lines, each of 11 serial cultures, one composed of human embryonic intestine and the other of brain. Additional experiments described in a preliminary manner are reported. Two objectives were in mind. One was to determine whether the Lansing strain was capable of multiplying in completely differentiated non-nervous tissue as well as in embryonic tissue, and the other was to determine whether the Brunhilde strain of poliomyelitis virus, which is immunologically distinct from the Lansing group and not adaptable to rodents, could, like the Lansing strain, be cultivated in embryonic human non-nervous tissues.

As a source of completely differentiated non-nervous tissue, fragments of human foreskin were employed. On the basis of the results from animal inoculations, the virus was maintained for 88 days through 5 serial cultures of human foreskin. It was calculated that during the 88-day period of cultivation the suspension of virus originally inoculated had undergone a dilution of at least 10^{-27}. It would appear, therefore, that the Lansing strain is capable of multiplication in the presence of well differentiated skin and subcutaneous tissue and in the absence of intact nerve cells.

Two series of experiments were initiated for the propagation of the Brunhilde strain utilizing the same technic. In one, the cultures consisted of mixed skin, muscle, and connective tissue from the extremities of human embryos of from 3 to 4 months gestation, and in the other brain tissue from the same embryos. In each, the original set of cultures was inoculated with 0.1 cc. of a 10 percent suspension of monkey cord infected with the Brunhilde strain of poliomyelitis virus. The findings resulting from animal inoculations indicate that the Brunhilde strain had been maintained for 73 days in the skin-muscle cultures and 39 days in those of brain. It was calculated that during the longer period the original inoculum of virus had been diluted 10^{-22} times as a result of subculture and changes in the fluid phase. According to Bodian the usual titer of monkey cord infected with this strain for the rhesus monkey is 10^{-6}. From the calculated dilution of the primary inoculum of the tissue cultures, it may, therefore, be inferred that this strain, like the Lansing virus, also multiplies in vitro in the presence of non-nervous tissue. Whether or not it can be propagated indefinitely under these conditions must await further investigation. (Proc. Soc. Exper. Biol. & Med., Oct. '49, T.H. Weller et al.)

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Current Morbidity for Poliomyelitis in USN: The incidence of acute anterior poliomyelitis among personnel of the Navy and Marine Corps has usually followed the seasonal trend found among the civilian population. Data have been compiled on the incidence of poliomyelitis in the service for the period January 1947 through September 1949, the latest month for which information is available. This material has been derived from the Monthly Morbidity Report (Navmed 582).

Cases of Poliomyelitis Taken Up on the Sick List Navy and Marine Corps

Month	1949	1948	1947
January	7	2	3
February	-	3	1
March	2	1	3
April	1	1	2
May	-	3	2
June	7	4	1
July	10	3	4
August	18	18	6
September	12	25	8
October		11	5
November		8	-
December		4	1
Total		83	36

Of particular interest this year is the unusual early start in the seasonal rise of poliomyelitis reported among personnel in the Navy and Marine Corps. The rise in the number of cases was more gradual, extending from June through August. There is shown in the table at the left the total new cases reported each month during the period under discussion. In addition to the early start in the rise in poliomyelitis this year as stated above, it may be noted that the number of cases reported did not quite reach the peaks shown in August and September 1948. The downward trend can be seen to start in September this year as compared to October in both 1947 and 1948. (Statistics of Navy Medicine for December 1949)

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Studies on the Pathogenisis of Experimental Necrotizing Arteritis: Previous studies in the authors' laboratory have shown that acute necrotizing arteritis can be produced with regularity in healthy adult dogs by feeding a specified high fat diet for a period of 8 weeks or longer then sacrificing them through renal damage. Three factors, diet, time, and renal damage, seem to be essential in the production of these lesions. Methods have been published in detail previously. The active dietary factor is found in cod liver oil but is apparently not unique to cod liver oil. The oil may be added to a kennel diet of unselected table scraps or to a standard diet, consisting of calves liver (raw wet weight), 32 parts, butter, 12 parts, and cod liver oil, 6 parts, with equal results. Renal damage has been produced by any one of 3 ways: (1) uranium nitrate subcutaneously, (2) mercuric chloride intravenously, and (3) bilateral nephrectomy; all are equally effective.

In all experiments to date, renal damage has been essential. To determine whether or not damage to tissues and organs other than the kidney would precipitate the arterial lesions in properly fed dogs, 2 series of experiments were undertaken. The experimental observations reaffirm the importance of the kidney in the pathogenisis of arterial lesions. All of the authors' results to date indicate that some derangement of renal function is prerequisite to the development of arterial lesions. Other workers have produced arterial lesions with various

pes of renal insufficiency, but none of these workers has found it necessary to ntrol the diet of his experimental animals. Whereas, in the authors' experience, standard renal insufficiency alone resulted in typical arterial lesions in ly 5 (4 percent) of 130 dogs; the combination of standard high fat diet and andard renal insufficiency resulted in typical arterial lesions in 36 (90 percent) of 40 dogs. This discrepancy between the authors' results incriminating dietary factor and the results of others ignoring a dietary factor may, in part, related to the definition of typical arterial lesions, for the authors do not nsider some of the hemorrhagic lesions illustrated in previous publications pical of their experimental lesions which are predominately necrotizing in aracter and only occasionally associated with gross hemorrhage.

If, as the above results indicate, standard high fat diet and standard renal sufficiency are both necessary for the production of typical arterial lesions, the oblem narrows down to what role the kidney plays in the metabolism of the potentially noxious fatty substance or substances contained in the specified high fat et. During the 2 months or more of high fat feeding, the kidneys become distended with sudanophilic material, the epithelial cells lining the loops of Henle d the distal portion of the proximal convoluted tubules are especially affected. his condition is still compatible with normal life, for the high fat diet can be d indefinitely and no predictable changes in the vascular system are ever observed unless the kidneys are damaged. Anytime after 2 months of such a diet andard renal insufficiency is regularly followed by typical arterial lesions. can be surmised that the intact kidney elaborated something necessary for e metabolism of the noxious lipids and that when the kidney is severely damged the noxious lipids or metabolic by-products thereof pile up to explosive vels as manifested by the arterial lesions.

The factor common to all the methods used for the production of standard nal insufficiency that have resulted in typical arterial lesions is massive damge to the proximal convoluted tubules in a relatively short period of time (massive coagulative necrosis with uranium nitrate and mercuric chloride and mass cclusion in the case of bilateral nephrectomy). The experiments reported in is paper show that severe damage to tissues and organs other than the kidneys es not precipitate arterial lesions in properly fed dogs and that bilateral eteral ligation, despite degrees of azotemia, phosphatemia, acidosis, and emia corresponding to those produced by standard renal insufficiency, is kewise ineffective in precipitating arterial lesions in properly fed dogs.

The simplest explanations that the authors have been able to formulate for ese unanticipated findings are: (1) the proximal convoluted tubules elaborate mething (lipase?) necessary for the proper utilization of certain lipid substances ; (2) the integrity of the proximal convoluted tubules is necessary for the neualization of certain toxic substances (amines?). These hypotheses are based in

large part upon the fact that 6 days after bilateral ureteral ligation the epithelium lining the proximal convoluted tubules is fairly well preserved whereas 6 days after standard renal insufficiency this epithelium appears to be almost completely destroyed. If these experimental findings are confirmed and if the reasoning is valid, the identification of these hypothetical substances (lipases ?, amines ?) might help clarify the relationship of the kidney to arterial lesions. (Proc. Soc. Exper. Biol. & Med., Oct '49, J.H. McCormick and R.L. Holman).

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Eighth Streptomycin Conference of the Veterans Administration, Army, and Navy: In the joint VA-Army-Navy Streptomycin Project, approximately 9 thousand (9000) patients with active tuberculosis have been treated with streptomycin (SM), dihydrostreptomycin (DHSM), para-aminosalicylic acid (PAS), and combinations of these agents. Twenty-three different regimens have been employed. The length of treatment and dosage used in these regimens has varied from 0.5 grams of SM or DHSM for 42 days to 2 grams of SM or DHSM for 120 days. The PAS dosage has remained constant at 12 grams per day. Interrupted regimens have been used in which SM or DHSM was administered every third or seventh day.

The combination of SM or DHSM with PAS produces a definitely superior therapeutic effect than does either of the 3 drugs administered alone. The optimum dosage and length of treatment is one gram of SM or DHSM plus 12 grams of PAS administered daily over a period of 120 days. There is little, if any, significant difference between the therapeutic effect noted with regimens employing SM as compared with DHSM. PAS alone is not as effective as either SM or DHSM. However, PAS will bring about some improvement in patients who have been previously treated with SM or DHSM and whose organisms are resistant to these antibiotics.

The antibiotics employed produce only a bacteriostatic effect and hence can not be used as definitive treatment. Because of this and the fact that approximately 99 percent of the patients treated were in either moderately or far advanced stages, the relapse rate following discontinuance of the antibiotics, has been high. Collapse therapy reduces the relapse rate from 33 percent to 25 percent in those patients followed from 13 to 24 months.

One of the greatest limitations to the use of SM or DHSM has been the fact that strains of Mycobacterium tuberculosis, resistant to these drugs develop in the majority of cases after 60 days of therapy. If effective control of the disease has not been accomplished in this relatively short period of time, relapse

is almost certain to occur and further use of SM or DHSM is without benefit. During the past year, combinations of the antibiotics have been used in an effort to delay the emergence of resistant organisms and thereby prolong the therapeutic effect. This has been accomplished most effectively by combining PAS with either SM or DHSM. On regimens employing SM or DHSM alone, approximately 66 percent of the patients showed resistant organisms after 90 days of therapy. With combined therapy of SM or DHSM plus PAS, only 10 percent of the patients treated showed resistant organisms after 90 days of therapy. The interrupted regimens in which SM or DHSM was employed at either 3 or 7 day intervals, produced some delay in resistance with very little loss of therapeutic effect.

The toxic effect of SM, based upon subjective vertigo or ataxia, was reduced from about 80 percent to 7 percent when the daily dose was reduced from 2 to one gram. DHSM in daily dosage of one gram gave slightly less vestibular disturbance than SM in the same dosage. When 2 grams or more of DHSM were administered, deafness occurred in a small percentage of cases. Deafness was insidious in onset and often appeared from 2 to 3 months after the drug was discontinued. This delayed toxic effect on the eighth cranial nerve was never seen with SM.

Drs. H. Corwin Hinshaw and Walsh McDermott were sent to Germany by the Schenley Laboratories to investigate TB-1 (Thiosemicarbazone). They visited 10 institutions in which 2,000 patients with tuberculosis had been treated with TB-1. Actually about 7,000 cases in all have been treated in Germany during the past 2 years. The drug has only recently been introduced into this country and basic in vitro and in vivo laboratory studies are now underway. Dr. Hinshaw's impression is that the drug has about the same therapeutic effect as PAS and it has a toxicity index for human beings slightly greater than PAS but less than SM. Limited studies will be carried out in patients in several of the hospitals in the Veterans Administration-Army-Navy study group. The drug will be available in ample quantities soon and will be inexpensive.

Neomycin acts against SM resistant organisms but is probably too toxic to have a wide application.

Mycomycin proved effective in protecting animals from tuberculous infection; however, the compound is highly unstable and must be kept at -70°F.; therefore it probably will not have wide application.

Several streptomycyclamines, (derivatives of SM) have been made. Although tuberculostatic, their action in the laboratory does not appear to be any better than SM and they are more costly to produce.

The Navy study unit formerly at Corona and now at San Diego has completed treatment on 45 patients employing a regimen of 2 grams of SM administered every 7 days over a period of 120 days. An additional 18 patients are now under treatment with 2 grams of SM every 7 days plus 12 grams of PAS daily, for a period of 120 days. It appears that the therapeutic result on the interrupted regimen with SM is slightly less than on the daily regimen. The main objective of this interrupted regimen was to determine whether or not a delay in the emergence of resistant organisms could be produced. The sensitivity studies are as yet incomplete. However, there is indication that there will be a definite delay in the emergence of resistant organisms. The laboratory studies are being carried out at the USNH, San Diego. Because the Navy unit is the only one in the cooperative group employing the interrupted regimen (SM once a week plus daily PAS) it was urged by the conference group that the study be continued and the series of patients treated be enlarged. (From material contained in the report by Commander R.O. Canada, MC, USN, who as BuMed's representative attended the conference held in Atlanta, Georgia, from the 10-13th of November 1949)

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Resistance of Mycobacterium Tuberculosis to Streptomycin: The resistance to streptomycin of a strain of Mycobacterium tuberculosis is now believed to be the result of selection, during the patient's treatment, of mutants which were already present in the original bacterial population. Although the proportion of resistant mutants in a population of sensitives has been estimated at less than 10 per 100,000 billion, they may be forefathers of a resistant race. Resistance appears when the innate properties of the mutant favor its survival and multiplication in an environment which becomes intolerable to its sensitive fellows. If resistance to streptomycin is thus undirected and spontaneous it is important to know whether it occurs, in a significant degree, among tuberculous patients who have never received the drug. Youmans and Karlson found that over 90 percent of 131 strains of M. tuberculosis from untreated patients were inhibited by less than 2 ug. of streptomycin per ml. of medium, and Mitchison, who examined 205 strains from 124 patients before treatment, reports a remarkably uniform susceptibility to the drug. These results must be set against such reports as that of the streptomycin committee of the American Veterans Association in 1948 which showed that 60 percent of cultures from patients who had been treated for 3 months were resistant to 10 or more ug. of streptomycin per ml. Mitchison has now examined nearly 400 resistant strains from treated patients and he finds that the strains fall into 3 groups, each with a characteristic degree of resistance. The organisms obtained from individual patients showed an abrupt change during treatment from sensitivity to one or other of the levels of resistance, and when this level was reached it was maintained through out treatment. One group of organisms was found by Mitchison to be only 4 times

less sensitive than that of the standard strain of M. tuberculosis, and it is obviously important to know whether or not the concentration of streptomycin in the patient's lesion is sufficient to deal with these slightly resistant strains. The present relatively crude sensitivity tests may not always detect such small degrees of resistance, and this may account for some of the failures in treatment when the infecting strain has been reported as sensitive.

The problem of streptomycin-resistant strains of M. tuberculosis is also being tackled from the prevention angle. It was shown in 1946 that the development in vitro of resistant strains could be retarded by adding diaminodiphenylsulfone to the medium, and Graessle and Pietrowski found that p-aminosalicylic acid (P.A.S.) acts in the same way. Karlson and others, at the Mayo Clinic, have now done periodic sensitivity tests on cultures of M. tuberculosis isolated from 14 patients being treated with combinations of streptomycin, P.A.S. and promin. At the end of 3 months of treatment streptomycin-resistant bacilli were found in only one patient, although after 6 months' treatment 3 additional patients also had resistant strains. These are encouraging if only provisional results, and it may well be that streptomycin and P.A.S. or some other form of combined therapy will keep the resistant mutant in its numerical place. (Lancet, 15 Oct. '49, Annotation)

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A Survey of the Accuracy of Rh Antibody Titrations in Several Hospital Laboratories: Because of the difficulties encountered by the author and coworkers in standardizing the materials and technic used in their Rh antibody titrations it was believed that it would be of value to survey the technic of several laboratories which also run this test routinely.

Upon inquiry, each laboratory was willing to submit its reports of titrations on duplicate bloods and to co-operate in a joint study. All members of the group fully understood the details of the survey and ran the tests on the submitted specimens exactly as they would on any routine blood for anti-Rh titer. Since then, the data presented here have been submitted to the participating laboratories, and the factors responsible for the observed discrepancies have been discussed and presumably corrected. Publication of these data seemed desirable. MacCready and McGee have pointed out the occurrence of unsuspected errors in routine Rh-typing in hospital laboratories. Their data indicate inaccuracy in a significant percentage of blood specimens tested for the Rh factor (about 7 percent of a series of almost 1500 Rh tests). Van Saun has emphasized the apparent lack of technical competency in many laboratories and has pointed out the desirability of a central public health laboratory taking over the responsibility for routine Rh-blood testing.

An examination of the reports submitted by the various laboratories that co-operated in this study indicates that laboratory A showed a few end points in the low range, particularly in saline medium. Laboratory A's results on the resubmitted specimens did not show satisfactory grouping. Although this laboratory claimed to have run a control with Rh-negative cells, it reported that the goat serum contained Rh antibodies. The reports of laboratory A are, therefore,considered to be inaccurate.

Laboratory B immediately noted agglutination with the animal serum against Rh-negative cells and inquired if this was an Hr serum. This laboratory made the logical response to the animal serum and their other end point values were satisfactory, although somewhat in the high range on the last specimens. This tendency was found to have been caused by a change of donors during the survey. The trend to higher values was recognized by the technician and she was planning to find a more suitable donor, or if possible, to return to the original donor. Furthermore, the reproducibility of results was satisfactory and it is considered that laboratory B was reliable.

Laboratory C did not routinely set its titrations up in saline medium. This is contrary to the usual practice and, in the experience of the author and co-workers, the changes in type of antibody are often as revealing as the absolute titration-end points. A patient with antibodies demonstrable only in albumin will often begin to show some activity in saline as term approaches if the baby is Rh-positive. Laboratory C submitted extremely low reports for approximately half of all the specimens, showed poor reproducibility on the duplicates, missed the antibodies entirely in specimen number 8, and reported the heteroagglutinins of the goat serum as Rh antibodies. The reports of laboratory C were believed to be of doubtful value.

Laboratory D also failed to detect the antibodies in specimen number 8 and reported the goat serum positive for Rh antibodies. The reports of this laboratory showed much variation and questionable reproducibility. It submitted a copy of its data sheet for each titration and an examination of these data showed atypical findings. A solid four plus clump will, in the experience of the author and co-workers, usually drop to a three plus or perhaps a two plus in the next higher dilution tube, but never to zero as was reported by that laboratory. It was difficult to decide exactly where its end point occurred because occasionally, after the agglutination had apparently been diluted out, the next higher dilution was reported as two plus. Apparently the tubes were being agitated too vigorously and the negatives were not checked under the microscope. This laboratory also considered the serum dilution after the blood suspension had been added; this is contrary to usual practice. For comparison the author and his co-workers have taken this into consideration and the reports of laboratory D

are based on serum dilutions before the addition of cell suspension. The reports of laboratory D were undoubtedly subject to serious technical error.

Laboratory E submitted end point figures which compared well with those of laboratories B and F. The goat serum showed tight four plus clumping both in saline and albumin with negative as well as positive cells and was, therefore, recognized as nonspecific. With one exception, the reproducibility of its results was satisfactory, and it detected the low-titered anti-Rh in specimen number 8.

Laboratory F did not receive all the specimens studied. The end points reported were apparently comparable with those submitted by laboratories B and E. With one possible exception, its end points were satisfactory.

The terminology of the cooperating laboratories was noted. Laboratory C employed the term "agglutination" but set its titers up in AB serum only and did not check for saline agglutinins. Laboratories A, B, and D employed the terms "agglutinating" and "conglutinating" for the Rh antibodies demonstrable with saline and albumin. The author and co-workers as well as laboratory F, employ the general term "agglutination" and qualify it as suggested by Davidsohn to indicate the particular medium employed, i.e., saline agglutinin or serum-albumin agglutinin. The use of the term "serum-albumin agglutinin" seems preferable to any other because this term clearly designates the type of test done. The term "blocking antibody" is not used by the author because this carries the connotation of blocking action, which is not being measured. The author and co-workers do not use the blocking test routinely nor does any other laboratory included in this survey. The descriptive terms "early immune" and "hyper-immune" originally proposed by Diamond for the saline-active and albumin-active antibodies are considered to be excellent and fitting, but the terms suggested by Davidsohn are perhaps more suitable from a technical point of view.

In reporting end points, laboratories A and D were employing the least amount of grossly-visible clumping as the end point, with the tendency to disregard any fine clumping, and laboratories B, C, and F were reading the end point microscopically. The author and co-workers have considered the end point as the very last dilution tube which shows grossly-visible agglutination. This is the "one plus" end point of the National Institutes of Health procedure and is more reproducible than the microscopic end point which may be found in the tube from one to 3 dilutions higher. In practice, the one plus tube as well as the tube with the next-higher dilution is always checked under the microscope to be sure of the positioning of the one-plus end point. Occasionally a titration will drop from a two plus to a plus-minus, in which case, the plus-minus is considered to be the end point. Two of the laboratories which reported some very low end points occasionally mentioned that rouleaux formation was present in these specimens in tubes of higher dilution. It is believed that they were confusing rouleaux formation with agglutination.

The medium employed by the cooperating laboratories for the demonstration of the serum-albumin agglutinin was also recorded. Laboratories A and F employed 20 percent bovine albumin, and laboratories C and D used AB serum. Laboratory B used the plasma from its standard cell donor, and the author and co-workers employed 30 percent bovine albumin mixed with an equal volume of AB serum. This mixture has been used in the author and co-workers laboratory for some time and they believe that it gives more clear-cut results than either medium alone; it seems to demonstrate Rh antibodies much better than does AB serum alone, and yet diminishes the occasional hemolysis and sticky trace of clumping caused by some lots of bovine albumin. Diamond and Denton have mentioned some of the objections to the use of plasma as a suspension medium. It does not seem that the different mediums employed by the several laboratories could have been a significant factor in explaining the variety of serum-albumin end points reported.

It is interesting that the end points submitted by the laboratories which apparently were technically correct showed so much variation. Both laboratories B and E detected the animal serum, both found the low titer on specimen number 8, and their groupings on the resubmitted specimens were comparatively excellent. However, an occasional end point reported by each of laboratories B, E, and F must necessarily be considered out of range of acceptable results. Thus it would appear that even under ideal conditions, an occasional titration will be unsatisfactory. It is interesting that the laboratories with unsatisfactory end points on the duplicate specimens were using random cells for their titrations. In the experience of the author and co-workers, not all donors are suitable and often several individuals must be examined before one is found whose cells will give an expected end point with a known antiserum and agglutination that is clear-cut. Furthermore, because most blood cells give decreasing titration end points as they age, the standard cells for titers should be less than 48 hours old. The practice of using random cells for Rh-antibody titrations should be discouraged.

When all technical details of the procedures have been carefully standardized, the variation between titration end points usually should not exceed one dilution tube. However, the author and co-workers no longer consider a trend between 2 titrations as significant until the end point continues to change to the next dilution tube in another titration. For example, if the end point changes from 1:16 to 1:32, they do not consider the titer as rising until a third determination gives an end point of 1:64. This emphasizes the need for determining the titer early in the pregnancy and following the titer at frequent intervals in patients who are known to be immunized. (Am. J. Clin. Path., Nov '49, R.W. Marsters)

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Preliminary Report on Quantitative Assays of Amino Acids in Human Dentin: As a result of studies made cooperatively over the past 3 years by LCDR Fred L. Losee, U. S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland and Dr. Walter C. Hess of Georgetown University Dental School, Washington, D. C., the relative quantities of 6 amino acids, histidine, lysine, arginine, cystine, methionine, and phenylalanine, present in the protein of human dentin, are reported, as shown below.

Assay Method	**Amino Acid Calculated as Present per 100 Grams of 16.0 Grams Nitrogen Protein**					
	Histidine	Lysine	Arginine	Cystine	Methionine	Phenylalanine
Microbiological: Henderson and Snell (modified)	1.0 gm	4.8 gm	6.8 gm			
Colorimetric: Hess and Sullivan				0.08 gm		
Hess and Sullivan (modified)					0.48 gm	
Hess and Sullivan						1.57 gm

The dentinal samples analyzed, highly selected for uniformity, were from freshly extracted teeth of patients 17 to 30 years of age. The teeth were erupted, permanent, noncarious, unstained first and second molars, with minimum pits and fissures, and almost uniform in color.

The researchers state that the results of these quantitative organic determinations are of value as part of the basic data by which theories regarding odontogenesis and pathological processes (e.g., caries) must be tested. Methods, definitions and materials will be described in detail at a later date.

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Communicable Disease Summaries for the U.S.:

For the Week Ended 26 November, 1949

Poliomyelitis. For the fourteenth consecutive week, total reported incidence of poliomyelitis in the Nation decreased over the preceding week. The total number of cases reported for the current week is 506 as compared with 755 last week. The 5-year median (1944-1948) for the fourty-seventh week is 229. Thirty-five States reported decreases ranging from one in 5 States to 43 in New York State. Ten States and the District of Columbia reported an aggregate increase of 57 cases, ranging from 1 case each in the District of Columbia and Delaware to 27 in Iowa. The current week is the highest reported by Iowa since October 1 when 56 cases were recorded. The total number of reported cases to date is 41,028 as compared with 26,215 for the corresponding period last year.

Other Communicable Diseases. No unusual incidence was reported in the Nation for the leading communicable diseases. One case of psittacosis was reported in California and one case of smallpox was reported in North Carolina. No cases of anthrax were reported. Diphtheria, influenza, measles, meningococcal meningitis, scarlet fever, typhoid fever, whooping cough, encephalitis, and tularemia decreased from the number reported last week. In addition, these diseases were below the 5-year median (1944-1948) for the current week. Three cases of Rocky Mountain spotted fever were reported as compared with two cases last week.

Rabies in Animals. Of 33 States reporting on rabies in animals, for 17 there were no cases. The remaining 16 States reported 87 cases with the largest numbers in New York (13) and Texas (22). The total number of rabies in animals reported to date is 5,103. For the calendar year 1948, 6,066 cases of rabies in animals were reported with the largest numbers in Texas (1,271), Indiana (805), Ohio (637), and New York (540). (Issued by National Office of Vital Statistics, U.S. Public Health Service, Federal Security Agency. Based upon preliminary reports by telegraph from State health officers)

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Study on CO Hazard from Parked Automobiles: Various types of fresh-air-intake vents used in connection with the heaters of many 1949 model automobiles are located under the radiator grill at the front of the car. It was suspected that the use of such equipment, when parked behind a car the motor of which was running, might produce a serious carbon monoxide hazard inside the rear car if its doors and windows were closed. To determine the extent

of this hazard, a number of cars of different makes, all using this type of heater, were tested. With doors and windows closed they were first parked bumper-to-bumper, with the distance between the cars increased after each test until no carbon monoxide was found inside the rear car.

When the cars were parked bumper-to-bumper, the highest concentration of carbon monoxide found in the test car at the end of one minute's time was 650 parts per million parts of air. Several readings of 300 parts per million were found. The lowest reading recorded at the end of one minute was 250 parts per million. With the test car parked 2 feet behind the car with the motor running, a high concentration of 300 parts per million was encountered at the end of one minute. After 2 minutes, a high reading of 950 parts per million and a low reading of 500 parts per million were recorded. At the end of 3 minutes' time, with the cars in the same position, a high reading of 1,500 parts per million was reached. This was the maximum that could be recorded with the testing instrument, and it is probable that the concentration was higher than that indicated.

Carbon monoxide concentrations of over 500 parts per million were found in all of the rear cars when parked as far as 4 feet behind the car with the motor running for 2 or 3 minutes. No carbon monoxide was found inside the test cars when the cars were separated by a distance of 8 feet. The concentrations found varied with the type of car parked in front. Less carbon monoxide was encountered behind some cars with flanged tailpipe extensions. Additionally, the tailpipes of some cars projected at an angle toward either the right or left and little carbon monoxide was encountered when the engines of such cars were run.

The results of these tests seem to indicate that a serious hazard exists when cars having the above-mentioned type of heater are parked under the conditions outlined. The instruction manuals of some of the car manufacturers contain a warning against the use of car heaters when parked behind another car. (Indust. Hyg. Newsletter, Nov. '49, H. I. Williams et al.)

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Eligibility Requirements of the American College of Hospital Administrators: BuMed has received information from the American College of Hospital Administrators that commanding officers and executive officers of naval hospitals are eligible to apply for membership in the college. See circular letter 49-159 on page 30.

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Course for Enlisted HC Personnel on Handling Radioactive Isotopes: A six-months' course of instruction in the handling and technical application of radioactive isotopes is currently being conducted for enlisted technicians of the Navy Medical Department at the Naval Medical School, National Naval Medical Center, Bethesda, Maryland.

The course covers the broad field of isotopes. The curriculum consists of the following subjects: general and radio chemistry, mathematics, outline of radiation, study of methods by which isotopes are prepared, administrative and laboratory procedures including use of Geiger counters, safety precautions, the use and care of equipment, scalers and tubes, survey meters used to detect radiation, and radioautographs.

The present class consists of five men who were selected from the recently graduating class of X-ray technicians.

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Law Course for Medical Officers: An unusual opportunity is available to medical officers of the Navy, for training in Law. The Bureau invites interested medical officers with the rank of Lieutenant or Lieutenant Commander in the regular Navy to apply for a course in legal training in an accredited law school in the District of Columbia, beginning in February or June 1950. Successful completion of the prescribed course leads to the award of the LL.B. degree. Application from officers whose interests are in the administrative field of military medicine are particularly desired. Those applicants who are selected will be ordered to the Bureau for duty and given additional duty orders under instruction. The course is of 3 years duration, instruction being given during nine of the 12 months of each year. Applicants must have a minimum of 5 years of prior active duty, of which 2 years must have been sea or foreign duty. The application must contain an agreement not to resign during the course of instruction or within 3 years after its completion. Inquiries concerning further details may be addressed to the Professional Division of the Bureau of Medicine and Surgery.

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Special Opportunity for Training and Experience in Leprosy Available: A Navy Medical Officer is now serving as Officer in Charge of the Provisional Leper Colony of the Trust Territory of the Pacific on Tinian, M. I. This officer will be eligible for rotation to duty in the continental United States in March 1950, and the Bureau is now giving thought to the selection of a suitable replacement. It is planned to assign the medical officer selected as replacement to a brief period of indoctrination at the Carville Leprosarium in Louisiana and thereafter to a period of similar training at the Leper Colony, Molakai, Territory of Hawaii.

The Bureau of Medicine and Surgery will be pleased to consider applications for this training and duty for Medical Officers (below the rank of Commander) who are desirous of furthering their training and experience in the general field of tropical medicine and in the study and care of leprous patients in particular.

The duration of duty in this area is approximately eighteen months. Government quarters are furnished. Extra pay in the amount of $100.00 per month for this duty is provided for under Section 204 of the new pay bill; this is over and above the $100.00 per month additional pay which medical and dental officers on active duty already receive.

Applications may be made by letter or dispatch and should reach BuMed as soon as possible. No service agreement is required. (Personnel Div., BuMed)

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BUMED CIRCULAR LETTER 49-157 25 November 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Handbook of the Hospital Corps, 1949 edition

1. The 1949 edition of the Handbook of the Hospital Corps has been printed and is being distributed to the service for the information of all Medical Department personnel.

2. This edition will provide Hospital Corps personnel with a compact manual for reference in the field. It is desired that the new Handbook be utilized as an adjunct to the 1939 edition, but not to replace it.

3. The Handbook of the Hospital Corps, 1939 edition, contains comprehensive information not included in the 1949 edition. Therefore until further notice the 1939 edition shall continue to be used as the basic text book in Hospital Corps Schools and for Hospital Corps Navy Standard Training Courses and Hospital Corps advancement examination questions.

4. The Handbook of the Hospital Corps, 1939 edition, may be ordered on NavMed Form 4, from the Navy Medical Supply Depots, Brooklyn, New York and Oakland, California under stock number 7-814-000. C. A. Swanson

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BUMED CIRCULAR LETTER 49-158 28 November 1949

From: Chief, Bureau of Medicine and Surgery
To: U. S. Naval Hospitals, U. S. Naval Medical Centers, and U. S. Naval Medical Supply Depots

Subj: Foremen Mechanics with Reduction in Force Notices - Consideration of for Future Vacancies

Encl: (1) Under SecNav ltr OIR-290-rnw of 3 Nov 1949

This letter (1) states that in accordance with enclosure no vacancy for Master or Foreman may be filled by promotion until consideration has been given to the qualifications of all Masters and Foremen whose separation through reduction in force occurred since 1 September 1949 or occurs at some future date; (2) states that it was required by the enclosure that each Bureau prepare and maintain a list containing the names of all such Masters and Foremen, including a record of their qualifications, and provide copies of these lists to each of the other Bureaus; and (3) gives procedures which are to be carried out by addresses until further notice, in order that BuMed may comply with the provisions of that enclosure.

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BUMED CIRCULAR LETTER 49-159 30 November 1949

From: Chief, Bureau of Medicine and Surgery
To: Medical Officers in Command, U. S. Naval Hospitals

Subj: American College of Hospital Administrators; membership in

1. Information has been received from the College of Hospital Administrators that Medical Officers in Command and Executive Officers of naval hospitals are eligible to apply for membership in the College.

2. The eligibility requirements of the College for candidates are as follows:

NOMINEE:

(a) Candidates who have a baccalaureate degree (based upon a four-year college course) from an educational institution approved by the American College of Hospital Administrators, or its equivalent in education and/or experience, who have had at least three years of successful experience in responsible hospital administrative positions, who hold such positions at the time of election, who in other respects meet the requirements prescribed for candidates by the Board of Regents and who indicate that it is their desire to prepare themselves for careers in hos pital administration.

(b) Candidates who have completed satisfactorily courses in hospital administration which are approved by the American College of Hospital Administrators, provided they are engaged in hospital administrative activities at the time of their election and in other respects meet the requirements prescribed for candidates by the Board of Regents.

The status of Nominees shall be limited to five years. Four years following their admission, Nominees eligible for advancement to Membership shall be requested to complete the prescribed procedure for such advancement before the conclusion of the fifth year or to sever their connection with the College at that time. Nominees, who by virtue of the fact that they are not eligible for Membership at the end of the five year period, and who otherwise are acceptable, shall be placed on the roster of Inactive Nominees.

MEMBERS:

(a) In order to qualify for election as a Member, the candidate must be the chief administrative officer or the assistant administrative officer of an approved hospital at the time of election and must have been a Nominee in good standing for at least two years, except that the Board of Regents in its discretion may elect directly, as Members, candidates found by the Credentials Committee to possess extraordinary qualifications beyond the intent of the Bylaws and regulations governing admission and advancement. Such a candidate must be the chief administrative officer of an approved hospital at the time of election.

FELLOWS:

(a) In order to qualify for election as a Fellow, the candidate must have been a Member in good standing for at least five years.

3. The Initiation Fees for members are as follows:

(a) For Fellows, when advancing from status of Member.....$25.00
(b) For Members, upon original admission.....$75.00
(c) For Members, advancing from status of Nominee to Member.$25.00
(d) For Nominees upon original admission..... $50.00

4. Application forms may be obtained from either the Bureau of Medicine and Surgery or the College of Hospital Administrators, 22 East Division Street, Chicago, 10, Illinois. The completed application form will be submitted to the Bureau of Medicine and Surgery for the Surgeon General's endorsement and forwarding to the College.

5. It is considered desirable that officers eligible for membership in this College avail themselves of this opportunity to be accepted in the organization.

C. A. Swanson

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NAVY DEPARTMENT
BUREAU OF MEDICINE AND SURGERY
WASHINGTON 25, D. C.

OFFICIAL BUSINESS

Permit No. 1048
NavMed-369 12/49

PENALTY FOR PRIVATE USE TO AVOID PAYMENT OF POSTAGE, $300